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INCREASING THE DISSOLUTION RATE OF SOME BENZOTHIADIAZINE DERIVATIVES BY SOLID AND LIQUID DISPERSION TECHNIQUES*

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ABSTRACT

Dissolution rates of water-insoluble drugs such as Chlorothiazide, Hydrochlorothiazide, Flumethiazide and Cyclopenthiazide were markedly increased when dispersed in polyethylene glycol 6000. The increased dissolution rate was believed to be attributed to the molecular and for the colloidal dispersion of the drug in the matrix of PEG 6000. Bendroflumethiazide and Methylclothiazide were found to be decomposed by either of dispersion techniques.

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INTRODUCTION

A number of modern therapeutic agents are poorly soluble in the aqueous fluids of the gastro-intestinal tract. Consequently, the in vivo dissolution rate of these compounds is low and their gastro-intestinal absorption tends to be incomplete and erratic (1). Since dissolution rate is directly proportional to the surface area (2), one may increase the rate by decreasing particle size of the drug. The greater the surface area, rapid the dissolution and thereby faster absorption, provided that the absorption is rate limited by the dissolution process. This reduction in the particle size has also limitation because of lot of factors, but formulation of a drug as a solid dispersion effectively causes a reduction in particle size. Enhancement of the rate of dissolution by this method, and thus possible absorption rate increase for poorly soluble drugs, has been shown by number of workers (3 - 11). Many water soluble carriers have been employed in these systems and new agents continue to be tested.

The purpose of this investigation was to compare the dissolution of some of the pure benzothiadiazine derivatives and dispersed mixture of the same, by solvent and melt dispersion techniques.

EXPERIMENTAL

Materials - The following materials were used:-

Drugs - Chlorothiazide, Hydrochlorothiazide, Bendroflumethiazide, Cyclopenthiazide, Methylclothiazide and Flumethiazide.

Carrier - Polyethylene glycol 6000.

All the materials and chemicals were obtained from standard sources and were of pharmaceutical grade.

Preparation of Samples - Dispersions with carrier and each drug were made by either solvent or melt method (depending on suitability of the process). Coprecipitates from solvent method were prepared by dissolving the carrier and each drug separately in sufficient acetone-methanol mixture (1:1) to fully solubilize the materials. The solvent was allowed to evaporate by stirring under ambient conditions. The last traces of the solvent were removed by heating the sample to constant weight at 45°. It was observed that some of the benzothiadiazines such as bendroflumethiazide and methylclothiazide were decomposed even when they were dried at 35°. The melts were prepared by heating a physical mixture of the drug, such as hydrochlorothiazide 10% and carrier PEG 6000, in a boiling tube over a hot oil bath. The melt was stirred until the

drug dissolved in the carrier and uniformity of the drug in the melt was attained. The melts were solidified by pouring on a clean and dry stainless steel plate.

It must be emphasized here that some of the dispersed mixtures prepared both by solvent dispersion technique and melt method either took too long time or never dried at all. The summary of the preparations is given in the table 1. The dispersions from both methods were pulverised in a mortar and those which passed through a mesh size 250 μm and retained on 75 μm were considered for further studies.

Stability Studies of Fused Mixtures - To test whether the drugs were decomposed by the fusion process, UV spectral characteristics of the pure and the processed samples were carried out. In the UV study the spectra of pure and dispersed drugs in 1% methanol solutions were scanned from 200 to 340 nm by recording PYE UNICHEM Spectrophotometer. For chromatographic studies strong ammonia solution and amyl alcohol (1:9) was used as the solvent. After developing the chromatograms by ascending technique, the spots were located by UV light (12).

Dissolution Rate Studies - Dissolution rates of pure and dispersed drugs were carried out in 100 ml.

distilled water at room temperature, using the USP XIX dissolution apparatus. The different amount of drugs were used, (Table 1). The pure drug or dispersed drug was placed in a cellulose bag and was suspended in the beaker containing water at 37°. The solution was stirred at a rate of 50 rpm. The solution was withdrawn at appropriate intervals and was replaced by equivalent amount of fresh distilled water.

The wave lengths used for measuring absorbance in the dissolution rate studies were as follows:- Chlorothiazide, 281 λm, hydrochlorothiazide, 317 λm, bendroflumethiazide, 274 λm, flumethiazide, 279 λm and methylclothiazide, 272 λm, respectively.

The concentration of drugs was calculated from the absorbance data according to established Beer's law plots. The presence of the carrier in this study did not affect the assays. All studies were run at least in duplicate. The dissolution characteristics of the solid dispersions were reproducible. A slightly higher but relatively insignificant variation was seen between runs of the pure compounds.

RESULTS AND DISCUSSION

Stability Studies - R_f values and U.V. spectra and molar extinction coefficient of pure and processed

TABLE 1a - FIFTY AND SEVENTY FIVE PERCENT DISSOLUTION TIMES
STABILITY AND OTHER CHARACTERISTICS OF BENZOTHIADIAZINE DERIVATIVES

Drug and Quantity (% w/w)	Carrier	Method	Nature of the Processed drug	Conc. in mg/ml For Dissolution	T_{50} (min.)	T_{75} (min.)
Chlorothiazide - 5	PEG 6000	Coprecipitate	Stable and dry powder	2.2	15	50
10	PEG 6000	Coprecipitate	Stable and dry powder	1.1	40	60
Pure substance				0.11	> 60	$\gg 60$
				0.44	> 60	-
Hydrochlorothiazide 5	PEG 6000	Melt	Stable and dry powder	5.9	5	8.5
10	PEG 6000	Melt and coprecipitate	did not dry completely up to 5 weeks			
Pure substance				0.295	> 60	$\gg 60$

TABLE 1b - FIFTY AND SEVENTY FIVE PERCENT DISSOLUTION TIMES
STABILITY AND OTHER CHARACTERISTICS OF BENZOTHIADIAZINE DERIVATIVES

Drug and Quantity (% w/w)	Carrier	Method	Nature of the Processed drug	Conc. in mg/ml For Dissolution	T_{50} (min.)	T_{75} (min.)
Flumethiazide 5	PEG 6000	Coprecipitate	Stable and dry powder	10	5	8
10	PEG 6000	Coprecipi-	Stable and dry	5	8	17
Pure substance				0.5	almost insoluble	-
				2	almost insoluble	
Cyclopenthiazide* 5	PEG 6000	Coprecipitate	Stable and dry powder	4	4	7
Pure substance				0.2	almost insoluble	-

Bendroflumethiazide & methylclothiazide were found to be unstable even after processing very carefully by both the dispersion techniques. *Only one combination was possible due to lack of pure substance.

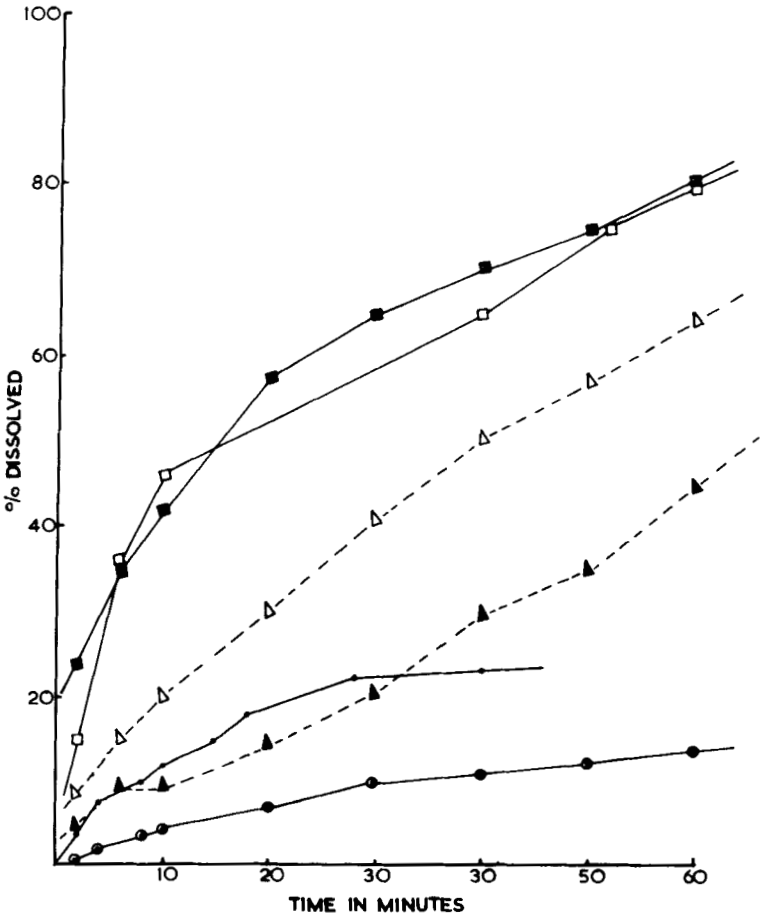

FIGURE 1.

Dissolution profiles of chlorothiazide and chlorothiazide PEG 6000 solid dispersions at 28°C. ● pure substance (0.11 mg/ml), ◑ pure substance (0.44 mg/ml), □ 5% co-ppt. (2.2 mg/ml); ■ 5% co.ppt. (8.8 mg/ml). ▲ 10% co-ppt. (1.1 mg/ml), ▲ 10% co-ppt (4.4 mg/ml).

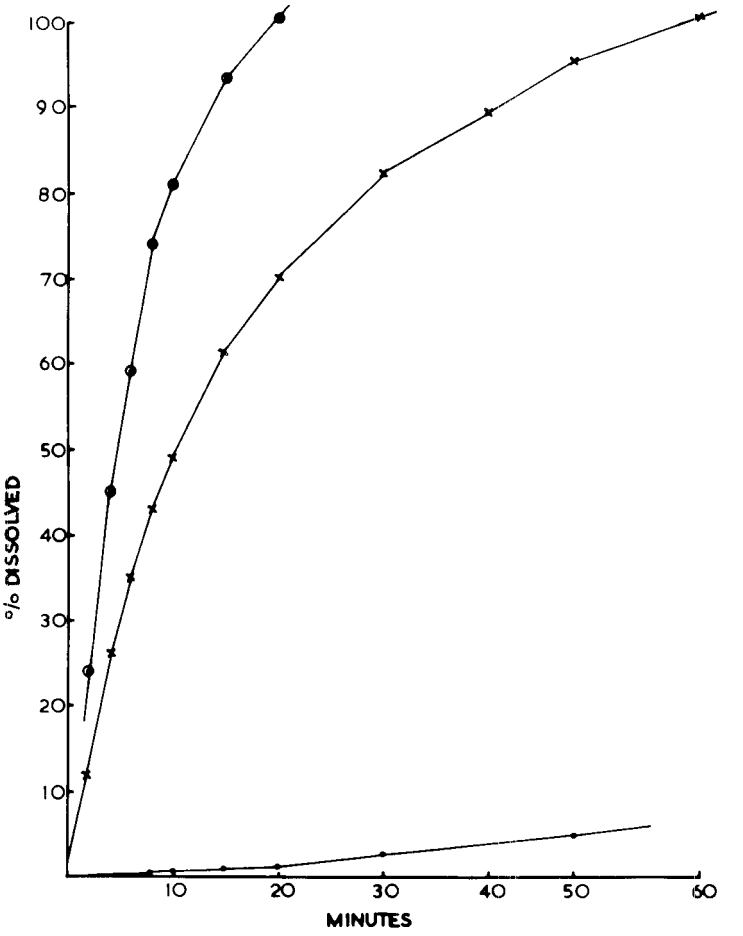

FIGURE 2

Dissolution profiles of hydrochlorothiazide and hydrochlorothiazide - PEG 6000 solid dispersions at 28° ● pure substance (0.295 mg/ml), ◑ 5% melt (5.9 mg/ml), × 5% melt (17.7 mg/ml).

drugs were identical within experimental error, indicating any lack of decomposition. However, both the melts and coprecipitates of bendroflumethiazide and methylclothiazide show decomposition detectable by U.V.

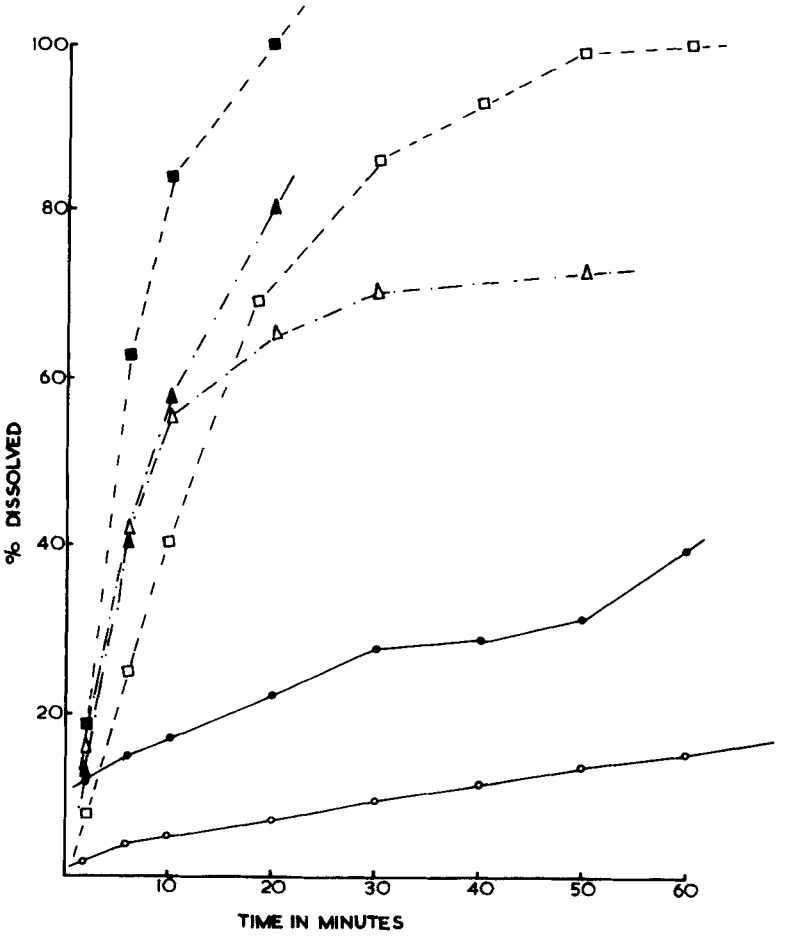

FIGURE 3

Dissolution profiles of flumethiazide and flumethiazide PEG 6000 solid dispersions at 28°. ● pure substance (0.5 mg/ml), ○ pure substance (2.0 mg/ml), ■ 5% co-ppt. (10 mg/ml), ▲ 5% co-ppt (40 mg/ml), □ 10% co-ppt (5 mg/ml) △ 10% co-ppt (20 mg/ml).

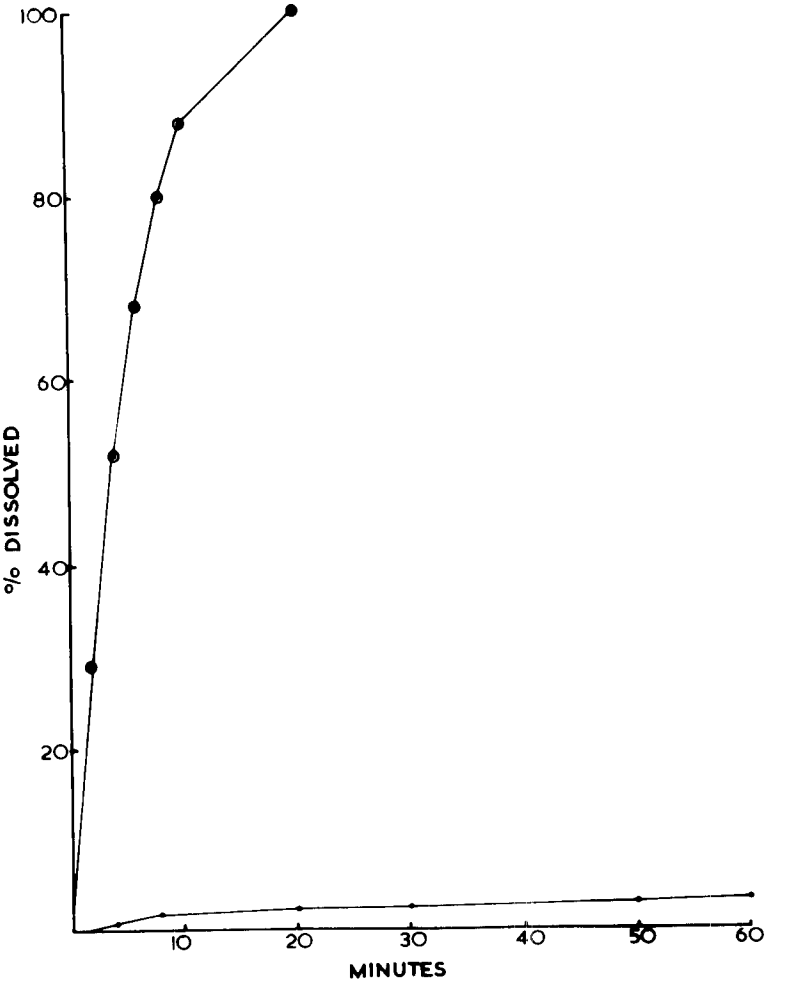

FIGURE 4

Dissolution profiles of cyclopenthiazide and cyclopenthiazide - PEG 6000 solid dispersions at 28°. ● pure substance (0.2 mg/ml), ◐ 5% melt (4 mg/ml).

spectra and by the presence of more than one spot on the paper chromatogram with different R_f values.

Dissolution Rate Studies - Figures 1 to 4 show excellent dissolution rates obtained by dispersion system with 5% dispersed drug in the system when half saturation dissolution test was applied. By super-saturation test method, all drugs in the dispersed system attained super-saturation in less than 10 minutes. The dissolution of the drugs from the powders of the same sieve was much slower, rather in certain cases it was almost insoluble. T_{50} was greater than 60 minutes in all the cases. The time required to disolve 50% (designated by T_{50}) of the four insoluble drugs was ranging from 4 to 15 minutes, and the time required to dissolve 75% (designated by T_{75}) was ranging from 7 to 50 minutes. There was an increase by almost 60 to 200% in T_{50} and 20 to 110% in T_{75} when the dispersed drug concentration was 10% as compared to 50%.

Although the exact physical nature of these dispersed systems was not investigated in this preliminary study, it is believed that the reduction of the particle size of the drug to the molecular level and/or colloidal level is the primary contributing factor for these phenomenon. This explanation is based on the theoretical considerations of molecular size difference

between the polymers and the drug and cooling and viscous effect of the drug - polyethylene glyco melt.

From these investigations and previous reports, one can accept the importance of polyethylene glycol polymers to serve as fast release carrier for poorly soluble drugs. It is also a good technique for incorporating the insoluble drug for faster absorption in the system.

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